REMARKS

This Amendment is in response to Examiner's Final Office Action mailed April 12, 2006 and Applicants' attorneys', Albert Halluin and Shirley X. Chen, Ph.D., telephone interview with Examiners Parithosh K. Tungaturthi, Ph.D. and Larry R. Helms, Ph.D. on June 13, 2006. Claims 1-25 and 30-31 are canceled without prejudice. Claims 26-29 are now pending.

Reconsideration is respectfully requested in view of the following remarks.

I. Interview with Examiners

Applicants express appreciation to Examiner Tungaturthi and Examiner Helms for conducting a telephone interview with Applicants on June 13, 2006. During the interview Applicants discussed the issues raised by the Examiner in the Final Office Action mailed April 12, 2006, details of which are described in the following sections.

I. Restriction Requirement

The Examiner states that claims 26-29 are drawn to a bispecfic tetravalent homodimeric antibody, and claims 30 and 31 are drawn to a method of producing said single-chain Fv monomer. As the inventions specified by claims 26-29 and claims 30-31 are two separate and distinct inventions according to the Examiner's Restriction Requirement maild June 10, 2005, pursuant to 37 C.F.R. §1.142 Applicants elect claims 26-29 without traverse. Accordingly, claims 30 and 31 are canceled without prejudice.

Pursuant to 35 U.S.C. §121 Applicants reserve the right to file one or more divisional applications directed to the non-elected inventions during the pendency of the present application.

II. Claim Rejections – 35 USC § 103(a)

Claims 26-29 stand rejected under 35 U.S. C. 103(a) as being unpatentable over Holliger et al. (U.S. Pat. No. 5,837,242) in view of Whitlow et al. (U.S. Pat. No. 5,856,456) and further in view of Csoka et al. (Leukemia (1996) 10:1765-1772).

Independent claim 26 specifies a bispecific tetravalent homodimeric F_v antibody. As depicted in Figure 1C, for example, the F_v antibody is a homodimer formed by a bispecific bivalent

single-chain F_v antibody having at least four variable domains, V_H-A, V_L-A , V_H-B, and V_L-B. In addition, peptide linker 1 and peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids and peptide linker 2 has about 3 to about 10 amino acids.

As discussed during the interview and in detail below, the claimed bispecific tetravalent homodimer formed by two single-chain Fv monomers (each having at least four variable domains) is completely different from the bispecific F_v diabody designs disclosed in Holliger et al.

Holliger et al. neither teaches nor suggests **a fusion polypeptide or a single chain Fv monomer comprising at least four variable domains**. In contrast, Holliger et al. discloses co-expressing two diabodies (e.g., VHA-VLB and VHB-VLA) separately as two gene products from a single expression vector. See Figure 9. Figure 7 illustrates cloning strategies for such a co-expression vector. As described in the specification of Holliger et al. and illustrated in Figure 9G, the two different gene cassettes VHA-VLB and VHB-VLA are separated by an intervening non-coding region (see, e.g., column 6, lines 42 to 56). Further, Example 14 which illustrates Route C of Fig. 7 clearly discloses that SEQ ID NO:102 separating the two gene cassettes of VHA-VLB and VHB-VLA contains two TAA stop codons preventing a continous transcription of the two VH-VL gene cassettes into one single fusion polypeptide (column 50, line 40). Thus, Holliger et al. discloses diabody heterodimers formed via **non-covalent association** of the two diabodies VHA-VLB and VHB-VLA **separately expressed** from the same vector.

As also discussed during the interview, Holliger et al. merely proposed **cross-linking 2 diabodies via disulphide bonds or thioether linkages**. Column 19, lines 45-59. In contrast, as specified in independent claim 29, the Fv monomer has V_H-A linked to V_L-B by peptide linker 1, V_L-B linked to V_H-B by peptide linker 2, and V_H-B linked to V_L-A by peptide linker 3, wherein peptide linker 1 and peptide linker 3 are a peptide bond or have about 1 to about 10 amino acids; and **peptide linker 2 has 3 to about 10 amino acids**. Thus, Holliger et al.'s proposed disulphide bonds or thioether linkages have **zero amino acid residue** in between VHA-VLB and VHB-VLA, thus not a peptide linker.

Further, Holliger et al. teaches away from a bispecific tetravalent **homodimeric** Fv antibody as claimed. Specifically, Holliger et al. teaches that "*homodimers* [of the diabodies] *will not form a functional antibody binding site*" (column 14, line 45; brackets added). Holliger et al. merely

discloses **heterodimeric** bispecific Fv antibodies made of two different VH-VL polypeptides (see, in particular, column 14, line 64 to column 15, line 7).

Finally, none of the secondary references cited, Whitlow et al. and Csoka et al., overcomes the deficiencies of Holliger et al, because they do not disclose or suggest a homodimeric bispecific antibody as specified in claim 29.

In view of the distinct structural and functional differences between the claimed invention and the antibodies disclosed in the cited references, Applicants submit that a prima facie case of obviousness has not been established under 35 USC §103(a). Withdrawal of this ground of rejection is therefore respectfully requested.

CONCLUSION

Applicants submit that this paper fully addresses the Office Action mailed April 12, 2006 and puts the claims 26-29 under condition for allowance. Should the Examiner have any questions, the Examiner is encouraged to contact the undersigned attorneys. The Commissioner is hereby authorized to charge any required fees due in connection with this submission, including petition and extension of time fees, and to credit any overpayment, to Deposit Account No. 23-2415 (Docket No. 31304-756.831).

Respectfully submitted,

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